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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 38/16, C07K 14/46		A1	(11) International Publication Number: WO 99/07404 (43) International Publication Date: 18 February 1999 (18.02.99)
(21) International Application Number: PCT/US98/16387 (22) International Filing Date: 6 August 1998 (06.08.98) (30) Priority Data: 60/055,404 8 August 1997 (08.08.97) US		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
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(54) Title: NOVEL EXENDIN AGONIST COMPOUNDS**(57) Abstract**

Novel exendin agonist compounds are provided. These compounds are useful in treating Type I and II diabetes and conditions which would be benefited by lower plasma glucose and delaying and/or slowing gastric emptying.

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DESCRIPTION**NOVEL EXENDIN AGONIST COMPOUNDS**

This application claims the benefit of U.S. Provisional Application No. 60/055,404, filed August 8, 1997, the contents of which are hereby incorporated by reference in their entirety.

5

Field of the Invention

The present invention relates to novel compounds which have activity as exendin agonists. These compounds are useful in treatment of Type I and II diabetes, in treatment of disorders which would be benefited by agents which lower plasma glucose levels and in treatment of disorders which would be benefited with agents useful in delaying and/or slowing gastric emptying.

10

BACKGROUND

The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art to the presently claimed invention, nor that any of the publications specifically or implicitly referenced are prior art to that invention.

15

Exendin

The exendins are peptides that are found in the venom of the Gila-monster, a lizard common in Arizona and Northern Mexico. Exendin-3 [SEQ. ID. NO. 1] is present in the venom of Heloderma horridum, and exendin-4 [SEQ. ID. NO. 2] is

present in the venom of *Heloderma suspectum* (Eng, J., et al., *J. Biol. Chem.*, 265:20259-62, 1990; Eng., J., et al., *J. Biol. Chem.*, 267:7402-05, 1992). The amino acid sequence of exendin-3 is shown in Figure 2. The amino acid sequence of exendin-4 is shown in Figure 3. The exendins have some sequence similarity to several members of the glucagon-like peptide family, with the highest homology, 53%, being to GLP-1[7-36]NH₂ [SEQ. ID. NO. 3] (Goke, et al., *J. Biol. Chem.*, 268:19650-55, 1993). GLP-1[7-36]NH₂, also known as 10 proglucagon[78-107] or simply, "GLP-1," has an insulinotropic effect, stimulating insulin secretion from pancreatic β -cells. The amino acid sequence of GLP-1 is shown in Figure 4. GLP-1 also inhibits glucagon secretion from pancreatic α -cells (Ørsov, et al., *Diabetes*, 42:658-61, 1993; D'Alessio, et al., *J. Clin. Invest.*, 97:133-38, 1996). GLP-1 is 15 reported to inhibit gastric emptying (Willms B, et al., *J. Clin. Endocrinol. Metab.* 81 (1): 327-32, 1996; Wettergren A, et al., *Dig Dis Sci* 38 (4): 665-73, 1993), and gastric acid secretion. Schjoldager BT, et al., *Dig Dis Sci* 34 (5): 7-20 03-8, 1989; O'Halloran DJ, et al., *J. Endocrinol.* 126 (1): 169-73, 1990; Wettergren A, et al., *Dig Dis Sci* 38 (4): 665-73, 1993). GLP-1[7-37], which has an additional glycine residue at its carboxy terminus, also stimulates insulin secretion in humans (Ørsov, et al., *Diabetes*, 42:658-61, 1993). A transmembrane G-protein adenylate-cyclase-coupled 25 receptor believed to be responsible for the insulinotropic effect of GLP-1 has been cloned from a β -cell line (Thorens, *Proc. Natl. Acad. Sci. USA* 89:8641-45 (1992)).

Exendin-4 reportedly acts at GLP-1 receptors on insulin-secreting β TC1 cells, at dispersed acinar cells from guinea pig pancreas, and at parietal cells from stomach; the peptide 30

is also said to stimulate somatostatin release and inhibit gastrin release in isolated stomachs (Goke, et al., J. Biol. Chem. 268:19650-55, 1993; Schepp, et al., Eur. J. Pharmacol., 269:183-91, 1994; Eissele, et al., Life Sci., 55:629-34, 1994). Exendin-3 and exendin-4 were reportedly found to stimulate cAMP production in, and amylase release from, pancreatic acinar cells (Malhotra, R., et al., Regulatory Peptides, 41:149-56, 1992; Raufman, et al., J. Biol. Chem. 267:21432-37, 1992; Singh, et al., Regul. Pept. 53:47-59, 1994). Based on their insulinotropic activities, the use of exendin-3 and exendin-4 for the treatment of diabetes mellitus and the prevention of hyperglycemia has been proposed (Eng, U.S. Patent No. 5,424,286).

Agents which serve to delay gastric emptying have found a place in medicine as diagnostic aids in gastro-intestinal radiologic examinations. For example, glucagon is a polypeptide hormone which is produced by the α cells of the pancreatic islets of Langerhans. It is a hyperglycemic agent which mobilizes glucose by activating hepatic glycogenolysis. It can to a lesser extent stimulate the secretion of pancreatic insulin. Glucagon is used in the treatment of insulin-induced hypoglycemia, for example, when administration of glucose intravenously is not possible. However, as glucagon reduces the motility of the gastro-intestinal tract it is also used as a diagnostic aid in gastro-intestinal radiological examinations. Glucagon has also been used in several studies to treat various painful gastro-intestinal disorders associated with spasm. Daniel, et al. (Br. Med. J., 3:720, 1974) reported quicker symptomatic relief of acute diverticulitis in patients treated with glucagon compared with those who had been

treated with analgesics or antispasmodics. A review by Glauser, et al., (J. Am. Coll. Emergency Physns, 8:228, 1979) described relief of acute esophageal food obstruction following glucagon therapy. In another study glucagon 5 significantly relieved pain and tenderness in 21 patients with biliary tract disease compared with 22 patients treated with placebo (M.J. Stower, et al., Br. J. Surg., 69:591-2, 1982).

Methods for regulating gastrointestinal motility using 10 amylin agonists are described in International Application No. PCT/US94/10225, published March 16, 1995.

Methods for regulating gastrointestinal motility using exendin agonists are described in a U.S. Patent Application Serial No. 08/908,867.

15 Certain exendin agonists are described in United States Provisional Application No. 60/065,442 filed November 14, 1997 and in United States Provisional Application Serial No. 60/066,029 filed November 14, 1997.

SUMMARY OF THE INVENTION

20 According to one aspect, the present invention provides novel exendin agonist compounds which exhibit advantageous properties which include effects in slowing gastric emptying and lowering plasma glucose levels.

According to the present invention, provided are compounds of the formula (I) [SEQ. ID. NO. 4]:

1 5 10
Xaa₁ Xaa₂ Xaa₃ Gly Thr Xaa₄ Xaa₅ Xaa₆ Xaa₇ Xaa₈
5 15 20
Ser Lys Gln Xaa₉ Glu Glu Glu Ala Val Arg Leu
 25 30
Xaa₁₀ Xaa₁₁ Xaa₁₂ Xaa₁₃ Leu Lys Asn Gly Gly Xaa₁₄
 35
10 Ser Ser Gly Ala Xaa₁₅ Xaa₁₆ Xaa₁₇ Xaa₁₈-Z

wherein Xaa₁ is His, Arg or Tyr; Xaa₂ is Ser, Gly, Ala or Thr; Xaa₃ is Asp or Glu; Xaa₄ is Phe, Tyr or naphthylalanine; Xaa₅ is Thr or Ser; Xaa₆ is Ser or Thr; Xaa₇ is Asp or Glu; Xaa₈ is Leu, Ile, Val, pentylglycine or Met; Xaa₉ is Leu, Ile, pentylglycine, Val or Met; Xaa₁₀ is Phe, Tyr or naphthylalanine; Xaa₁₁ is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met; Xaa₁₂ is Glu or Asp; Xaa₁₃ is Trp, Phe, Tyr, or naphthylalanine; Xaa₁₄, Xaa₁₅, Xaa₁₆ and Xaa₁₇, are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine; Xaa₁₈ is Ser, Thr or Tyr; and Z is -OH or -NH₂; with the proviso that the compound does not have the formula of either SEQ. ID. NOS. 1 or 2. Also included within the scope of the present invention are pharmaceutically acceptable salts of the compounds of formula (I) and pharmaceutical compositions including said compounds and salts thereof.

Also provided are compounds of the formula (II)
[SEQ. ID. NO. 36] :

1 5 10
5 Xaa₁ Xaa₂ Xaa₃ Gly Thr Xaa₄ Xaa₅ Xaa₆ Xaa₇ Xaa₈
 15 20
 Ser Lys Gln Xaa₉ Glu Glu Ala Val Arg Leu
 25 30
 Xaa₁₀ Xaa₁₁ Xaa₁₂ Xaa₁₃ Leu X₁ Gly Gly Xaa₁₄
10 35
 Ser Ser Gly Ala Xaa₁₅ Xaa₁₆ Xaa₁₇ Xaa₁₈-Z

wherein Xaa₁ is His, Arg, Tyr or 4-imidazopropionyl; Xaa₂ is Ser, Gly, Ala or Thr; Xaa₃ is Asp or Glu; Xaa₄ is Phe, Tyr or naphthylalanine; Xaa₅ is Thr or Ser; Xaa₆ is Ser or Thr; Xaa₇ is Asp or Glu; Xaa₈ is Leu, Ile, Val, pentylglycine or Met; Xaa₉ is Leu, Ile, pentylglycine, Val or Met; Xaa₁₀ is Phe, Tyr or naphthylalanine; Xaa₁₁ is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met; Xaa₁₂ is Glu or Asp; Xaa₁₃ is Trp, Phe, Tyr, or naphthylalanine; X₁ is Lys Asn, Asn Lys, Lys-NH^e-R Asn, Asn Lys-NH^e-R where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl or cycloalkylalkanoyl; Xaa₁₄, Xaa₁₅, Xaa₁₆ and Xaa₁₇ are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine; Xaa₁₈ is Ser, Thr or Tyr; and Z is -OH or -NH₂; with the proviso that the compound does not have the formula of either SEQ. ID. NOS. 1 or 2. Also included within the scope of the present invention are pharmaceutically acceptable salts of the compounds of formula (II) and pharmaceutical compositions including said compounds and salts thereof.

30 Definitions

In accordance with the present invention and as used

herein, the following terms are defined to have the following meanings, unless explicitly stated otherwise.

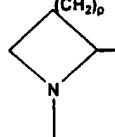
The term "amino acid" refers to natural amino acids, unnatural amino acids, and amino acid analogs, all in their D and L stereoisomers if their structure allow such stereoisomeric forms. Natural amino acids include alanine (Ala), arginine (Arg), asparagine (Asn), aspartic acid (Asp), cysteine (Cys), glutamine (Gln), glutamic acid (Glu), glycine (Gly), histidine (His), isoleucine (Ile), leucine (Leu), 10 Lysine (Lys), methionine (Met), phenylalanine (Phe), proline (Pro), serine (Ser), threonine (Thr), typtophan (Trp), tyrosine (Tyr) and valine (Val). Unnatural amino acids include, but are not limited to azetidinecarboxylic acid, 2-amino adipic acid, 3-amino adipic acid, beta-alanine, 15 aminopropionic acid, 2-aminobutyric acid, 4-aminobutyric acid, 6-aminocaproic acid, 2-aminoheptanoic acid, 2-aminoisobutyric acid, 3-aminoisobutyric acid, 2-aminopimelic acid, tertiary-butylglycine, 2,4-diaminoisobutyric acid, desmosine, 2,2'-diaminopimelic acid, 2,3-diaminopropionic acid, N-ethylglycine, N-ethylasparagine, homoproline, 20 hydroxylysine, allo-hydroxylysine, 3-hydroxyproline, 4-hydroxyproline, isodesmosine, allo-isoleucine, N-methylalanine, N-methylglycine, N-methylisoleucine, N-methylpentylglycine, N-methylvaline, naphthalanine, 25 norvaline, norleucine, ornithine, pentylglycine, pipecolic acid and thioproline. Amino acid analogs include the natural and unnatural amino acids which are chemically blocked, reversibly or irreversibly, or modified on their N-terminal amino group or their side-chain groups, as for example, 30 methionine sulfoxide, methionine sulfone, S-(carboxymethyl)-cysteine, S-(carboxymethyl)-cysteine sulfoxide and S-

(carboxymethyl)-cysteine sulfone.

The term "amino acid analog" refers to an amino acid wherein either the C-terminal carboxy group, the N-terminal amino group or side-chain functional group has been

5 chemically codified to another functional group. For example, aspartic acid-(beta-methyl ester) is an amino acid analog of aspartic acid; N-ethylglycine is an amino acid analog of glycine; or alanine carboxamide is an amino acid analog of alanine.

10 The term "amino acid residue" refers to radicals having the structure: (1) $-\text{C}(\text{O})-\text{R}-\text{NH}-$, wherein R typically is $-\text{CH}(\text{R}')-$, wherein R' is an amino acid side chain, typically H or a carbon containing substituent;

or (2)  , wherein p is 1, 2 or 3 representing the

15 azetidinecarboxylic acid, proline or pipecolic acid residues, respectively.

The term "lower" referred to herein in connection with organic radicals such as alkyl groups defines such groups with up to and including about 6, preferably up to and 20 including 4 and advantageously one or two carbon atoms. Such groups may be straight chain or branched chain.

25 "Pharmaceutically acceptable salt" includes salts of the compounds of the present invention derived from the combination of such compounds and an organic or inorganic acid. In practice the use of the salt form amounts to use of the base form. The compounds of the present invention are

useful in both free base and salt form, with both forms being considered as being within the scope of the present invention.

In addition, the following abbreviations stand for the following:

- "ACN" or "CH₃CN" refers to acetonitrile.
- "Boc", "tBoc" or "Tboc" refers to t-butoxy carbonyl.
- "DCC" refers to N,N'-dicyclohexylcarbodiimide.
- "Fmoc" refers to fluorenylmethoxycarbonyl.
- "HBTU" refers to 2-(1H-benzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate.
- "HOBt" refers to 1-hydroxybenzotriazole monohydrate.
- "homOP" or "hPro" refers to homoproline.
- "MeAla" or "Nme" refers to N-methylalanine.
- "naph" refers to naphthylalanine.
- "pG" or "pGly" refers to pentylglycine.
- "tBuG" refers to tertiary-butylglycine.
- "ThioP" or "tPro" refers to thioproline.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the amino acid sequences for certain compounds of the present invention [SEQ. ID. NOS. 5 TO 35].

Figure 2 depicts the amino acid sequence for exendin-3 [SEQ. ID. NO. 1].

Figure 3 depicts the amino acid sequence for exendin-4 [SEQ. ID. NO. 2].

Figure 4 depicts the amino acid sequence for GLP-1 [SEQ. ID. NO. 3].

Figure 5 depicts dose dependent effects of exendin-4 in comparison with compound 1 of Figure 1 [SEQ. ID. NO. 5] on

plasma glucose levels in db/db mice.

Figure 6 depicts a comparison of effects on gastric emptying of exendin-4, exendin-4 acid and compound 1 of Figure 1 [SEQ. ID. NO. 5].

5

DETAILED DESCRIPTION OF THE INVENTION

Preferred Compounds

According to the present invention, provided are compounds of the formula (I) [SEQ. ID. NO. 4]:

1 5 10
10 Xaa₁ Xaa₂ Xaa₃ Gly Thr Xaa₄ Xaa₅ Xaa₆ Xaa₇ Xaa₈
 15 20
Ser Lys Gln Xaa₉ Glu Glu Glu Ala Val Arg Leu
 25 30
Xaa₁₀ Xaa₁₁ Xaa₁₂ Xaa₁₃ Leu Lys Asn Gly Gly Xaa₁₄
15 35
Ser Ser Gly Ala Xaa₁₅ Xaa₁₆ Xaa₁₇ Xaa₁₈-Z

wherein Xaa₁ is His, Arg or Tyr; Xaa₂ is Ser, Gly, Ala or Thr; Xaa₃ is Asp or Glu; Xaa₄ is Phe, Tyr or naphthylalanine; Xaa₅ is Thr or Ser; Xaa₆ is Ser or Thr; Xaa₇ is Asp or Glu; Xaa₈ is Leu, Ile, Val, pentylglycine or Met; Xaa₉ is Leu, Ile, pentylglycine, Val or Met; Xaa₁₀ is Phe, Tyr or naphthylalanine; Xaa₁₁ is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met; Xaa₁₂ is Glu or Asp; Xaa₁₃ is Trp, Phe, Tyr, or naphthylalanine; Xaa₁₄, Xaa₁₅, Xaa₁₆ and Xaa₁₇ are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine; Xaa₁₈ is Ser, Thr or Tyr; and Z is -OH or -NH₂; with the proviso that the compound does not have the formula of either SEQ. ID. NOS. 1 or 2. Preferred N-alkyl groups for N-alkylglycine, N-alkylpentylglycine and N-alkylalanine include lower alkyl groups preferably of 1 to about 6 carbon atoms, more preferably of 1 to 4 carbon atoms. Suitable compounds of

formula (I) include those having amino acid sequences of SEQ. ID. NOS. 5 to 35.

Preferred exendin agonist compounds of formula (I) include those wherein Xaa₁ is His or Tyr. More preferably Xaa₁ is His. Preferred are those such compounds wherein Xaa₂ is Gly. Preferred are those such compounds wherein Xaa₃ is Leu, pentylglycine or Met.

Preferred compounds of formula (I) include those wherein Xaa₁₃ is Trp or Phe.

Also preferred are compounds of formula (I) wherein Xaa₄ is Phe or naphthylalanine; Xaa₁₁ is Ile or Val and Xaa₁₄, Xaa₁₅, Xaa₁₆ and Xaa₁₇ are independently selected from Pro, homoproline, thioproline or N-alkylalanine. Preferably N-alkylalanine has a N-alkyl group of 1 to about 6 carbon atoms. According to an especially preferred aspect, Xaa₁₅, Xaa₁₆ and Xaa₁₇ are the same amino acid residue.

Preferred are compounds of formula (I) wherein Xaa₁₈ is Ser or Tyr, more preferably Ser.

Preferably Z is -NH₂.

According to one aspect, preferred are compounds of formula (I) wherein Xaa₁ is His or Tyr, more preferably His; Xaa₂ is Gly; Xaa₄ is Phe or naphthylalanine; Xaa₃ is Leu, pentylglycine or Met; Xaa₁₀ is Phe or naphthylalanine; Xaa₁₁ is Ile or Val; Xaa₁₄, Xaa₁₅, Xaa₁₆ and Xaa₁₇ are independently selected from Pro, homoproline, thioproline or N-alkylalanine; and Xaa₁₈ is Ser or Tyr, more preferably Ser. More preferably Z is -NH₂.

According to an especially preferred aspect, especially preferred compounds include those of formula (I) wherein: Xaa₁ is His or Arg; Xaa₂ is Gly; Xaa₃ is Asp or Glu; Xaa₄ is

Phe or naphthylalanine; Xaa₅ is Thr or Ser; Xaa₆ is Ser or Thr; Xaa₇ is Asp or Glu; Xaa₈ is Leu or pentylglycine; Xaa₉ is Leu or pentylglycine; Xaa₁₀ is Phe or naphthylalanine; Xaa₁₁ is Ile, Val or t-butyltylglycine; Xaa₁₂ is Glu or Asp; Xaa₁₃ is 5 Trp or Phe; Xaa₁₄, Xaa₁₅, Xaa₁₆, and Xaa₁₇, are independently Pro, homoproline, thioproline, or N-methylalanine; Xaa₁₈ is Ser or Tyr; and Z is -OH or -NH₂; with the proviso that the compound does not have the formula of either SEQ. ID. NOS. 1 or 2. More preferably Z is -NH₂. Especially preferred 10 compounds of formula (I) include those having the amino acid sequence of SEQ. ID. NOS. 5, 6, 17, 18, 19, 22, 24, 31, 32 and 35.

According to an especially preferred aspect, provided 15 are compounds of formula (I) where Xaa₉ is Leu, Ile, Val or pentylglycine, more preferably Leu or pentylglycine, and Xaa₁₃ is Phe, Tyr or naphthylalanine, more preferably Phe or naphthylalanine. These compounds will exhibit advantageous duration of action and be less subject to oxidative 20 degradation, both *in vitro* and *in vivo*, as well as during synthesis of the compound.

Also provided are compounds of the formula (II) [SEQ. ID. NO. 36]:

1	5	10										
Xaa ₁	Xaa ₂	Xaa ₃	Gly	Thr	Xaa ₄	Xaa ₅	Xaa ₆	Xaa ₇	Xaa ₈			
25					15				20			
	Ser	Lys	Gln	Xaa ₉	Glu	Glu	Glu	Ala	Val	Arg	Leu	
					25					30		
				Xaa ₁₀	Xaa ₁₁	Xaa ₁₂	Xaa ₁₃	Leu	X ₁	Gly	Gly	Xaa ₁₄
					35							
30				Ser	Ser	Gly	Ala	Xaa ₁₅	Xaa ₁₆	Xaa ₁₇	Xaa ₁₈	-Z

wherein Xaa_1 is His, Arg, Tyr or 4-imidazopropionyl; Xaa_2 is Ser, Gly, Ala or Thr; Xaa_3 is Asp or Glu; Xaa_4 is Phe, Tyr or naphthylalanine; Xaa_5 is Thr or Ser; Xaa_6 is Ser or Thr; Xaa_7 is Asp or Glu; Xaa_8 is Leu, Ile, Val, pentylglycine or Met; 5 Xaa_9 is Leu, Ile, pentylglycine, Val or Met; Xaa_{10} is Phe, Tyr or naphthylalanine; Xaa_{11} is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met; Xaa_{12} is Glu or Asp; Xaa_{13} is Trp, Phe, Tyr, or naphthylalanine; X_1 is Lys Asn, Asn Lys, Lys-NH^e-R Asn, Asn Lys-NH^e-R where R is Lys, Arg, C₁-C₁₀ straight chain 10 or branched alkanoyl or cycloalkylalkanoyl; Xaa_{14} , Xaa_{15} , Xaa_{16} and Xaa_{17} are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine; Xaa_{18} is Ser, Thr or Tyr; and Z is -OH or -NH₂; with the proviso that the compound does not have the formula 15 of either SEQ. ID. NOS. 1 or 2. Also included within the scope of the present invention are pharmaceutically acceptable salts of the compounds of formula (II) and pharmaceutical compositions including said compounds and salts thereof. Suitable compounds of formula (II) include that compound 20 having the amino acid sequences of SEQ. ID. NOS. 37-40.

Preferred exendin agonist compounds of formula (II) include those wherein Xaa_1 is His, Tyr or 4-imidazopropionyl. More preferably, Xaa_1 is His or 4-imidazopropionyl.

Preferred are those compounds of formula (II) wherein 25 Xaa_2 is Gly.

Preferred are those compounds of formula (II) wherein Xaa_3 is Leu, pentylglycine or Met.

Preferred are those compounds of formula (II) wherein Xaa_{13} is Trp or Phe.

30 Preferred are those compounds of formula (II) wherein

X₁ is Lys Asn, or Lys-NH^e-R Asn, where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl.

Also preferred are compounds of formula (II) wherein Xaa₁ is Phe or naphthylalanine; Xaa₁₀ is Phe or naphthylalanine; Xaa₁₁ is Ile or Val and Xaa₁₄, Xaa₁₅, Xaa₁₆ and Xaa₁₇ are independently selected from Pro, homoproline, thioproline or N-alkylalanine. According to an especially preferred aspect, Xaa₁₈ is Ser or Tyr. Preferred are those such compounds wherein Xaa₁₈ is Ser. Preferably, Z is -NH₂.

According to one preferred aspect, preferred are compounds of formula (II) wherein Xaa₄ is Phe or naphthylalanine; Xaa₁₀ is Phe or naphthylalanine; Xaa₁₁ is Ile or Val, X₁ is Lys Asn, or Lys-NH^e-R Asn, where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl and Xaa₁₄, Xaa₁₅, Xaa₁₆ and Xaa₁₇ are independently selected from Pro, homoproline, thioproline or N-alkylalanine.

The compounds referenced above form salts with various inorganic and organic acids and bases. Such salts include salts prepared with organic and inorganic acids, for example, HCl, HBr, H₂SO₄, H₃PO₄, trifluoroacetic acid, acetic acid, formic acid, methanesulfonic acid, toluenesulfonic acid, maleic acid, fumaric acid and camphorsulfonic acid. Salts prepared with bases include ammonium salts, alkali metal salts, e.g., sodium and potassium salts, and alkali earth salts, e.g., calcium and magnesium salts. Acetate, hydrochloride, and trifluoroacetate salts are preferred. The salts may be formed by conventional means, as by reacting the free acid or base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such

as water which is then removed in vacuo or by freeze-drying or by exchanging the ions of an existing salt for another ion on a suitable ion exchange resin.

Utility

5 The compounds described above are useful in view of their pharmacological properties. In particular, the compounds of the invention are exendin agonists, and possess activity as agents to regulate gastric motility and to slow gastric emptying, as evidenced by the ability to reduce post-prandial glucose levels in mammals.

Preparation of Compounds

The compounds of the present invention may be prepared using standard solid-phase peptide synthesis techniques and preferably an automated or semiautomated peptide synthesizer.

15 Typically, using such techniques, an α -N-carbamoyl protected amino acid and an amino acid attached to the growing peptide chain on a resin are coupled at room temperature in an inert solvent such as dimethylformamide, N-methylpyrrolidinone or methylene chloride in the presence of coupling agents such as dicyclohexylcarbodiimide and 1-hydroxybenzotriazole in the presence of a base such as diisopropylethylamine. The α -N-carbamoyl protecting group is removed from the resulting peptide-resin using a reagent such as trifluoroacetic acid or piperidine, and the coupling reaction repeated with the next 20 desired N-protected amino acid to be added to the peptide chain. Suitable N-protecting groups are well known in the art, with

25 t-butyloxycarbonyl (tBoc) and fluorenylmethoxycarbonyl (Fmoc)

being preferred herein.

The solvents, amino acid derivatives and 4-methylbenzhydryl-amine resin used in the peptide synthesizer may be purchased from Applied Biosystems Inc.

5 (Foster City, CA). The following side-chain protected amino acids may be purchased from Applied Biosystems, Inc.: Boc-Arg(Mts), Fmoc-Arg(Pmc), Boc-Thr(Bzl), Fmoc-Thr(t-Bu), Boc-Ser(Bzl), Fmoc-Ser(t-Bu), Boc-Tyr(BrZ), Fmoc-Tyr(t-Bu), Boc-Lys(Cl-Z), Fmoc-Lys(Boc), Boc-Glu(Bzl), Fmoc-Glu(t-Bu), Fmoc-His(Trt), Fmoc-Asn(Trt), and Fmoc-Gln(Trt). Boc-His(BOM) may
10 be purchased from Applied Biosystems, Inc. or Bachem Inc. (Torrance, CA). Anisole, dimethylsulfide, phenol, ethanedithiol, and thioanisole may be obtained from Aldrich Chemical Company (Milwaukee, WI). Air Products and Chemicals
15 (Allentown, PA) supplies HF. Ethyl ether, acetic acid and methanol may be purchased from Fisher Scientific (Pittsburgh, PA).

Solid phase peptide synthesis may be carried out with an automatic peptide synthesizer (Model 430A, Applied Biosystems
20 Inc., Foster City, CA) using the NMP/HOBt (Option 1) system and tBoc or Fmoc chemistry (see, Applied Biosystems User's Manual for the ABI 430A Peptide Synthesizer, Version 1.3B July 1, 1988, section 6, pp. 49-70, Applied Biosystems, Inc., Foster City, CA) with capping. Boc-peptide-resins may be
25 cleaved with HF (-5°C to 0°C, 1 hour). The peptide may be extracted from the resin with alternating water and acetic acid, and the filtrates lyophilized. The Fmoc-peptide resins may be cleaved according to standard methods (Introduction to Cleavage Techniques, Applied Biosystems, Inc., 1990, pp. 6-12). Peptides may be also be assembled using an Advanced
30

Chem Tech Synthesizer (Model MPS 350, Louisville, Kentucky).

Peptides may be purified by RP-HPLC (preparative and analytical) using a Waters Delta Prep 3000 system. A C4, C8 or C18 preparative column (10 μ , 2.2 x 25 cm; Vydac,

5 Hesperia, CA) may be used to isolate peptides, and purity may be determined using a C4, C8 or C18 analytical column (5 μ , 0.46 x 25 cm; Vydac). Solvents (A=0.1% TFA/water and B=0.1% TFA/CH₃CN) may be delivered to the analytical column at a flowrate of 1.0 ml/min and to the preparative column at 15 ml/min. Amino acid analyses may be performed on the Waters 10 Pico Tag system and processed using the Maxima program.

Peptides may be hydrolyzed by vapor-phase acid hydrolysis (115°C, 20-24 h). Hydrolysates may be derivatized and analyzed by standard methods (Cohen, et al., The Pico Tag

15 Method: A Manual of Advanced Techniques for Amino Acid Analysis, pp. 11-52, Millipore Corporation, Milford, MA (1989)). Fast atom bombardment analysis may be carried out by M-Scan, Incorporated (West Chester, PA). Mass calibration may be performed using cesium iodide or cesium 20 iodide/glycerol. Plasma desorption ionization analysis using time of flight detection may be carried out on an Applied Biosystems Bio-Ion 20 mass spectrometer. Electrospray mass spectroscopy may be carried and on a VG-Trio machine.

Peptide compounds useful in the invention may also 25 be prepared using recombinant DNA techniques, using methods now known in the art. See, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2d Ed., Cold Spring Harbor (1989). Non-peptide compounds useful in the present invention may be prepared by art-known methods.

30 The compounds referenced above may form salts with

various inorganic and organic acids and bases. Such salts include salts prepared with organic and inorganic acids, for example, HCl, HBr, H₂SO₄, H₃PO₄, trifluoroacetic acid, acetic acid, formic acid, methanesulfonic acid, toluenesulfonic acid, maleic acid, fumaric acid and camphorsulfonic acid.

5 Salts prepared with bases include ammonium salts, alkali metal salts, e.g., sodium and potassium salts, and alkali earth salts, e.g., calcium and magnesium salts. Acetate, hydrochloride, and trifluoroacetate salts are preferred. The

10 salts may be formed by conventional means, as by reacting the free acid or base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed in vacuo or by freeze-drying

15 or by exchanging the ions of an existing salt for another ion on a suitable ion exchange resin.

Formulation and Administration

Compounds of the invention are useful in view of their exendin-like effects, and may conveniently be provided in the

20 form of formulations suitable for parenteral (including intravenous, intramuscular and subcutaneous) or nasal or oral administration. In some cases, it will be convenient to provide an exendin or exendin agonist and another anti-gastric-emptying agent, such as glucagon, an amylin, or an

25 amylin agonist, in a single composition or solution for administration together. In other cases, it may be more advantageous to administer another anti-emptying agent separately from said exendin or exendin agonist. In yet other cases, it may be beneficial to provide an exendin or an

exendin agonist either co-formulated or separately with other glucose lowering agents such as insulin. A suitable administration format may best be determined by a medical practitioner for each patient individually. Suitable 5 pharmaceutically acceptable carriers and their formulation are described in standard formulation treatises, e.g., Remington's Pharmaceutical Sciences by E.W. Martin. See also Wang, Y.J. and Hanson, M.A. "Parenteral Formulations of Proteins and Peptides: Stability and Stabilizers," Journal of 10 Parenteral Science and Technology, Technical Report No. 10, Supp. 42:2S (1988).

Compounds useful in the invention can be provided as parenteral compositions for injection or infusion. They can, for example, be suspended in an inert oil, suitably a 15 vegetable oil such as sesame, peanut, olive oil, or other acceptable carrier. Preferably, they are suspended in an aqueous carrier, for example, in an isotonic buffer solution at a pH of about 5.6 to 7.4. These compositions may be sterilized by conventional sterilization techniques, or may 20 be sterile filtered. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH buffering agents. Useful buffers include for example, sodium acetate/acetic acid buffers. A form of repository or "depot" 25 slow release preparation may be used so that therapeutically effective amounts of the preparation are delivered into the bloodstream over many hours or days following transdermal injection or delivery.

The desired isotonicity may be accomplished using sodium 30 chloride or other pharmaceutically acceptable agents such as

dextrose, boric acid, sodium tartrate, propylene glycol, polyols (such as mannitol and sorbitol), or other inorganic or organic solutes. Sodium chloride is preferred particularly for buffers containing sodium ions.

5 The claimed compounds can also be formulated as pharmaceutically acceptable salts (e.g., acid addition salts) and/or complexes thereof. Pharmaceutically acceptable salts are non-toxic salts at the concentration at which they are administered. The preparation of such salts can facilitate 10 the pharmacological use by altering the physical-chemical characteristics of the composition without preventing the composition from exerting its physiological effect. Examples of useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration 15 and increasing the solubility to facilitate the administration of higher concentrations of the drug.

Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, hydrochloride, phosphate, sulfamate, acetate, citrate, lactate, tartrate, 20 methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, 25 tartaric acid, malonic acid, methanesulfonic acid, ethane-sulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclohexylsulfamic acid, and quinic acid. Such salts may be prepared by, for example, reacting the free acid or base forms of the product with one or more equivalents of the 30 appropriate base or acid in a solvent or medium in which the

salt is insoluble, or in a solvent such as water which is then removed in vacuo or by freeze-drying or by exchanging the ions of an existing salt for another ion on a suitable ion exchange resin.

5 Carriers or excipients can also be used to facilitate administration of the compound. Examples of carriers and excipients include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, 10 polyethylene glycols and physiologically compatible solvents. The compositions or pharmaceutical composition can be administered by different routes including intravenously, intraperitoneal, subcutaneous, and intramuscular, orally, topically, or transmucosally.

15 If desired, solutions of the above compositions may be thickened with a thickening agent such as methyl cellulose. They may be prepared in emulsified form, either water in oil or oil in water. Any of a wide variety of pharmaceutically acceptable emulsifying agents may be employed including, for 20 example, acacia powder, a non-ionic surfactant (such as a Tween), or an ionic surfactant (such as alkali polyether alcohol sulfates or sulfonates, e.g., a Triton).

25 Compositions useful in the invention are prepared by mixing the ingredients following generally accepted procedures. For example, the selected components may be simply mixed in a blender or other standard device to produce a concentrated mixture which may then be adjusted to the final concentration and viscosity by the addition of water or thickening agent and possibly a buffer to control pH or an 30 additional solute to control tonicity.

For use by the physician, the compounds will be provided in dosage unit form containing an amount of an exendin agonist, with or without another anti-emptying agent.

Therapeutically effective amounts of an exendin agonist for use in the control of gastric emptying and in conditions in which gastric emptying is beneficially slowed or regulated are those that decrease post-prandial blood glucose levels, preferably to no more than about 8 or 9 mM or such that blood glucose levels are reduced as desired. In diabetic or glucose intolerant individuals, plasma glucose levels are higher than in normal individuals. In such individuals, beneficial reduction or "smoothing" of post-prandial blood glucose levels, may be obtained. As will be recognized by those in the field, an effective amount of therapeutic agent will vary with many factors including the age and weight of the patient, the patient's physical condition, the blood sugar level or level of inhibition of gastric emptying to be obtained, and other factors.

Such pharmaceutical compositions are useful in causing gastric hypomotility in a subject and may be used as well in other disorders where gastric motility is beneficially reduced.

The effective daily anti-emptying dose of the compounds will typically be in the range of 0.01 or 0.03 to about 5 mg/day, preferably about 0.01 or 0.5 to 2 mg/day and more preferably about 0.01 or 0.1 to 1 mg/day, for a 70 kg patient, administered in a single or divided doses. The exact dose to be administered is determined by the attending clinician and is dependent upon where the particular compound lies within the above quoted range, as well as upon the age,

weight and condition of the individual. Administration should begin at the first sign of symptoms or shortly after diagnosis of diabetes mellitus. Administration may be by injection, preferably subcutaneous or intramuscular. Orally active compounds may be taken orally, however dosages should be increased 5-10 fold.

Generally, in treating or preventing elevated, inappropriate, or undesired post-prandial blood glucose levels, the compounds of this invention may be administered to patients in need of such treatment in a dosage ranges similar to those given above, however, the compounds are administered more frequently, for example, one, two, or three times a day.

The optimal formulation and mode of administration of compounds of the present application to a patient depend on factors known in the art such as the particular disease or disorder, the desired effect, and the type of patient. While the compounds will typically be used to treat human patients, they may also be used to treat similar or identical diseases in other vertebrates such as other primates, farm animals such as swine, cattle and poultry, and sports animals and pets such as horses, dogs and cats.

To assist in understanding the present invention the following Examples are included which describe the results of a series of experiments. The experiments relating to this invention should not, of course, be construed as specifically limiting the invention and such variations of the invention, now known or later developed, which would be within the purview of one skilled in the art are considered to fall within the scope of the invention as described herein and

hereinafter claimed.

EXAMPLE 1

Preparation of amidated peptide having SEQ. ID. NO. [5]

5 The above-identified peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.). In general, single-coupling cycles were used throughout the 10 synthesis and Fast Moc (HBTU activation) chemistry was employed. However, at some positions coupling was less efficient than expected and double couplings were required. In particular, residues Asp₅, Thr, and Phe₆ all required double coupling. Deprotection (Fmoc group removal) of the 15 growing peptide chain using piperidine was not always efficient. Double deprotection was required at positions Arg₂₀, Val₁₉, and Leu₁₄. Final deprotection of the completed peptide resin was achieved using a mixture of triethylsilane (0.2 mL), ethanedithiol (0.2 mL), anisole (0.2 mL), water (0.2 mL) and trifluoroacetic acid (15 mL) according to 20 standard methods (Introduction to Cleavage Techniques, Applied Biosystems, Inc.) The peptide was precipitated in ether/water (50 mL) and centrifuged. The precipitate was reconstituted in glacial acetic acid and lyophilized. The 25 lyophilized peptide was dissolved in water). Crude purity was about 55%.

Used in purification steps and analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

The solution containing peptide was applied to a

preparative C-18 column and purified (10% to 40% Solvent B in Solvent A over 40 minutes). Purity of fractions was determined isocratically using a C-18 analytical column. Pure fractions were pooled furnishing the above-identified 5 peptide. Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.5 minutes. Electrospray Mass Spectrometry (M): calculated 4131.7; found 4129.3.

10

EXAMPLE 2Preparation of Peptide having SEQ. ID. NO. [6]

The above-identified peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-15 protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 25% to 75% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an 20 observed retention time of 21.5 minutes. Electrospray Mass Spectrometry (M): calculated 4168.6; found 4171.2.

EXAMPLE 3Preparation of Peptide having SEQ. ID. NO. [7]

The above-identified peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 17.9 minutes. Electrospray Mass Spectrometry (M): calculated 4147.6; found 4150.2.

EXAMPLE 4

Preparation of Peptide having SEQ. ID. NO. [81]

The above-identified peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 35% to 65% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 19.7 minutes. Electrospray Mass Spectrometry (M): calculated 4212.6; found 4213.2.

EXAMPLE 5Preparation of Peptide having SEQ. ID. NO. [9]

The above-identified peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide
5 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 50% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 16.3 minutes. Electrospray Mass Spectrometry (M): calculated 4262.7; found 4262.4.

EXAMPLE 6Preparation of Peptide having SEQ. ID. NO. [10]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4172.6

EXAMPLE 7Preparation of Peptide having SEQ. ID. NO. [11]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide 5 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 10 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4224.7.

15

EXAMPLE 8Preparation of Peptide having SEQ. ID. NO. [12]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide 20 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 25 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4172.6

EXAMPLE 9Preparation of Peptide having SEQ. ID. NO. [13]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 5 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the 10 retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4186.6

EXAMPLE 10Preparation of Peptide having SEQ. ID. NO. [14]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved 20 from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the 25 lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4200.7

EXAMPLE 11Preparation of Peptide having SEQ. ID. NO. [15]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 5 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the 10 retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4200.7

EXAMPLE 12Preparation of Peptide having SEQ. ID. NO. [16]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved 20 from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 25 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4202.7.

EXAMPLE 13Preparation of Peptide having SEQ. ID. NO. [17]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide
5 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 10 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4145.6.

EXAMPLE 14Preparation of Peptide having SEQ. ID. NO. [18]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide
15 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 20 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4184.6.

EXAMPLE 15Preparation of Peptide having SEQ. ID. NO. [19]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide
5 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 10 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M) : calculated 4145.6.

15

EXAMPLE 16Preparation of Peptide having SEQ. ID. NO. [20]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide
20 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 25 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M) : calculated 4224.7.

EXAMPLE 17Preparation of Peptide having SEQ. ID. NO. [21]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 5 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the 10 retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4172.6.

EXAMPLE 18Preparation of Peptide having SEQ. ID. NO. [22]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved 20 from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 25 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4115.5.

EXAMPLE 19Preparation of Peptide having SEQ. ID. NO. [23]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide
5 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 10 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4188.6.

EXAMPLE 20Preparation of Peptide having SEQ. ID. NO. [24]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved
20 from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the
25 retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4131.6.

EXAMPLE 21Preparation of Peptide having SEQ. ID. NO. [25]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide
5 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 10 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4172.6.

EXAMPLE 22Preparation of Peptide having SEQ. ID. NO. [26]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide
15 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 20 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4145.6.

EXAMPLE 23Preparation of Peptide having SEQ. ID. NO. [27]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide
5 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the thioproline positions 38, 37, 36 and 31. Used in analysis are
10 Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated
15 4266.8.

EXAMPLE 24Preparation of Peptide having SEQ. ID. NO. [28]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide
20 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the thioproline positions 38, 37 and 36. Used in analysis are
25 Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then

carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4246.8.

EXAMPLE 25

5 Preparation of Peptide having SEQ. ID. NO. [29]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved 10 from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the homoproline positions 38, 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in 15 Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4250.8.

EXAMPLE 26

20 Preparation of Peptide having SEQ. ID. NO. [30]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved 25 from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the

homoproline positions 38, 37, and 36. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4234.8.

EXAMPLE 27

Preparation of Peptide having SEQ. ID. NO. [31]

10 The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the thioproline positions 38, 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4209.8.

EXAMPLE 28

Preparation of Peptide having SEQ. ID. NO. [32]

25 The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide

norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the 5 homoproline positions 38, 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product 10 peptide. Electrospray Mass Spectrometry (M): calculated 4193.7.

EXAMPLE 29

Preparation of Peptide having SEQ. ID. NO. [33]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide 15 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the N- 20 methylalanine positions 38, 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product 25 peptide. Electrospray Mass Spectrometry (M): calculated 3858.2.

EXAMPLE 30Preparation of Peptide having SEQ. ID. NO. [34]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide
5 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the N-methylalanine positions 38, 37 and 36. Used in analysis are
10 Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated
15 3940.3.

EXAMPLE 31Preparation of Peptide having SEQ. ID. NO. [35]

The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide
20 norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the N-methylalanine positions 38, 37, 36 and 31. Used in analysis
25 are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then

carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3801.1.

EXAMPLE 32

5 Preparation of Peptide having SEQ. ID. NO. [36]

4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys-NH^eoctanoyl Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH₂ [SEQ. ID. NO. 36] is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the 10 proline positions 38, 37, 36 and 31. Fmoc-Lys-NH^eoctanoyl acid is used for coupling at position 27. Instead of using 15 protected His for the final coupling at position 1, 4-imidazolylpropionic acid is coupled directly to the N-terminus of residues 2-39 on the resin. Used in analysis are 20 Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then 25 carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4294.5.

EXAMPLE 33Preparation of Peptide having SEQ. ID. NO. [37]

4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Asp
Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu
5 Phe Leu Lys-NH^eoctanoyl Asn Gly Gly Pro Ser Ser Gly Ala Pro
Pro Pro Ser-NH₂ [SEQ. ID. NO. 37] is assembled on 4-(2'-4'-
dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide
norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-
protected amino acids (Applied Biosystems, Inc.), cleaved
10 from the resin, deprotected and purified in a similar way to
Example 1. Additional double couplings are required at the
proline positions 38, 37, 36 and 31. Fmoc-Lys-NH^eoctanoyl acid
is used for coupling at position 27. Instead of using
protected His for the final coupling at position 1, 4-
15 imidazolylpropionic acid is coupled directly to the N-
terminus of residues 2-39 on the resin. Used in analysis are
Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in
ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in
Solvent A over 30 minutes) of the lyophilized peptide is then
20 carried out to determine the retention time of the product
peptide. Electrospray Mass Spectrometry (M): calculated
4242.7.

EXAMPLE 34Preparation of Peptide having SEQ. ID. NO. [38]

4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Asp
Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu
Trp Leu Asn Lys-NH^eoctanoyl Gly Gly Pro Ser Ser Gly Ala Pro

Pro Pro Ser-NH₂ [SEQ. ID. NO. 38] is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the proline positions 38, 37, 36 and 31. Fmoc-Lys-NH^eoctanoyl acid is used for coupling at position 28. Instead of using protected His for the final coupling at position 1, 4-imidazolylpropionic acid is coupled directly to the N-terminus of protected residues 2-39 on the resin. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4294.5.

EXAMPLE 35

20 Preparation of Peptide having SEQ. ID. NO. [39]

4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Asn Lys-NH^eoctanoyl Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH₂ [SEQ. ID. NO. 39] is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the

proline positions 38, 37, 36 and 31. Fmoc-Lys-NH⁶octanoyl acid is used for coupling at position 28. Instead of using protected His for the final coupling at position 1, 4-imidazolylpropionic acid is coupled directly to the N-terminus of residues 2-39 on the resin. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 10 4242.7.

EXAMPLE 36

Preparation of C-terminal carboxylic acid Peptides corresponding to the above C-terminal amide sequences.

The above peptides of Examples 1 to 35 are assembled on the so called Wang resin (p-alkoxybenzylalcohol resin (Bachem, 0.54 mmole/g)) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, 20 deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time 25 of the product peptide. Electrospray Mass Spectrometry provides an experimentally determined (M).

EXAMPLES A TO DReagents Used

GLP-1 was purchased from Bachem (Torrance, CA), all other peptides were prepared in house using synthesis methods such as those described therein. All chemicals were of the highest commercial grade. The cAMP SPA immunoassay was purchased from Amersham. The radioligands were purchased from New England Nuclear (Boston, MA). RINm5f cells (American Type Tissue Collection, Rockville, MD) were grown in DME/F12 medium containing 10% fetal bovine serum and 2mM L-glutamine. Cells were grown at 37°C and 5% CO₂/95% humidified air and medium was replaced every 2 to 3 days. Cells were grown to confluence then harvested and homogenized using on a Polytron homogenizer. Cell homogenates were stored frozen at -70°C until used.

Example AGLP-1 Receptor Binding Studies

Receptor binding was assessed by measuring displacement of [¹²⁵I] human GLP-1 (7-36) or [¹²⁵I] Exendin (9-39) from RINm5f membranes. Assay buffer contained 5 µg/ml bestatin 1 µg.ml phosphoramidon, 1 mg/ml bovine serum albumin (fraction V), 1 mg/ml bacitracin, and 1 mM MgCl₂, in 20 mM HEPES, pH 7.4. To measure binding, 30 µg membrane protein (Bradford protein assay) was resuspended in 200 µl assay buffer and incubated with 60 pM [¹²⁵I] human GLP-1 or Exendin (9-39) and unlabeled peptides for 120 minutes at 23°C in 96 well plates (Nagle Nunc, Rochester, NY). Incubations were terminated by rapid filtration with cold phosphatebuffered saline, pH 7.4,

through polyethyleneimine-treated GF/B glass fiber filters (Wallac Inc., Gaithersburg, MD) using a Tomtec Mach II plate harvester (Wallac Inc., Gaithersburg, MD). Filters were dried, combined with scintillant, and radioactivity 5 determined in a Betaplate liquid scintillant counter (Wallac Inc.).

Peptide samples were run in the assay as duplicate points at 6 dilutions over a concentration range of 10^{-6} M to 10^{-12} M to generate response curves. The biological activity 10 of a sample is expressed as an IC_{50} value, calculated from the raw data using an iterative curve-fitting program using a 4-parameter logistic equation (Prism, GraphPAD Software).

Example B

Cyclase Activation Study

15 Assay buffer contained 10 μ M GTP, 0.75 mM ATP, 2.5 mM $MgCl_2$, 0.5mM phosphocreatine, 12.5 U/ml creatine kinase, 0.4 mg/ml aprotinin, 1 μ M IBMX in 50 mM HEPES, pH 7.4. Membranes and peptides were combined in 100 ml of assay buffer in 96 well filter-bottom plates (Millipore Corp., Bedford, MA). 20 After 20 minutes incubation at 37°C, the assay was terminated by transfer of supernatant by filtration into a fresh 96 well plate using a Millipore vacuum manifold. Supernatant cAMP contents were quantitated by SPA immunoassay.

Peptide samples were run in the assay as triplicate 25 points at 7 dilutions over a concentration range of 10^{-6} M to 10^{-12} M to generate response curves. The biological activity of a particular sample was expressed as an EC_{50} value, calculated as described above. Results are tabulated in Table I.

TABLE I

Activity in the RINm5f cyclase assay

		EC ₅₀
5	Exendin-4 [SEQ. ID. NO. 2]	0.23
	Compound 1 [SEQ. ID. NO. 5]	0.17
	Compound 2 [SEQ. ID. NO. 6]	0.23
	Compound 3 [SEQ. ID. NO. 7]	0.42

Example C10 Determination of Blood Glucose Levels in db/db Mice - 1 Hour Protocol

15 C57BL/6J-m=/⁺Lepr^{db} mice, at least 3 months of age were utilized for the study. The mice were obtained from The Jackson Laboratory and allowed to acclimate for at least one week in the vivarium. Mice were housed in groups of ten at 22° ±1°C with a 12:12 light:dark cycle, with lights on at 6 a.m.

20 All animals were deprived of food for 2 hours before taking baseline blood samples. Approximately 100 µl of blood was drawn from each mouse via eye puncture, after a light anesthesia with metophane. After collecting baseline blood samples, to measure plasma glucose concentrations, all animals receive subcutaneous injections of either vehicle, exendin-4 or test compound in concentrations indicated.

25 Blood samples were drawn again, using the same procedure,

after exactly one hour from the injections, and plasma glucose concentrations were measured.

For each animal, the % change in plasma value, from baseline value, was calculated and a dose dependent relationship was evaluated using Graphpad Prism™ software.

Figure 5 depicts the effects of varying doses of exendin-4 and Compound 1 of Figure 1 [SEQ. ID. NO. 5] on plasma glucose levels.

Example D

10 The following study was carried out to examine the effects of exendin-4, exendin-4 acid and an exendin agonist (Compound 1 of Figure 1 [SEQ. ID. NO. 5]) on gastric emptying in rats. This experiment followed a modification of the method of Scarpignato, et al., Arch. Int. Pharmacodyn. Ther. 15 246:286-94 (1980).

Male Harlan Sprague Dawley (HSD) rats were used. All animals were housed at 22.7 ± 0.8 C in a 12:12 hour light:dark cycle (experiments being performed during the light cycle) and were fed and watered *ad libitum* (Diet LM-485, Teklad, 20 Madison, WI). Exendin-4 and exendin-4 acid were synthesized according to standard peptide synthesis methods. The preparation of Compound 1 [SEQ. ID. NO. 5] is described in Example 1.

25 The determination of gastric emptying by the method described below was performed after a fast of ~20 hours to ensure that the stomach contained no chyme that would interfere with spectrophotometric absorbance measurements.

Conscious rats received by gavage, 1.5ml of an acaloric gel containing 1.5% methyl cellulose (M-0262, Sigma Chemical

Co, St Louis, MO) and 0.05% phenol red indicator. Twenty minutes after gavage, rats were anesthetized using 5% halothane, the stomach exposed and clamped at the pyloric and lower esophageal sphincters using artery forceps, removed and 5 opened into an alkaline solution which was made up to a fixed volume. Stomach content was derived from the intensity of the phenol red in the alkaline solution, measured by absorbance at a wavelength of 560 nm. In separate experiments on 7 rats, the stomach and small intestine were 10 both excised and opened into an alkaline solution. The quantity of phenol red that could be recovered from the upper gastrointestinal tract within 20 minutes of gavage was 89±4%; dye which appeared to bind irrecoverably to the gut luminal surface may have accounted for the balance. To account for a 15 maximal dye recovery of less than 100%, percent of stomach contents remaining after 20 min were expressed as a fraction of the gastric contents recovered from control rats sacrificed immediately after gavage in the same experiment. Percent gastric contents remaining = (absorbance at 20 20 min) / (absorbance at 0 mm) x 100.

In baseline studies, with no drug treatment, gastric emptying over 20 min was determined. In dose-response studies, rats were treated with 0.01, 0.1, 0.3, 1, 10 and 100 μ g of exendin-4, 0.01, 0.03, 0.1, 1, 10 and 100 μ g exendin-4 acid, and 0.1, 0.3, 1, 10 and 100 μ g of Compound 1 [SEQ. ID. 25 NO. 5].

The results are shown in Figure 6. The results, shown in Figure 6 and Table II, show that the exendin agonists, exendin-4 acid and compound 1 are potent inhibitors of 30 gastric emptying. The EC₅₀ of exendin-4 was 0.27 μ g. The

EC₅₀s of exendin-4 acid and Compound 1 were comparable (0.12 µg and 0.29 µg, respectively).

TABLE II

Compound	EC ₅₀ (µg)
exendin-4	0.27
exendin-4 acid	0.12
Compound 1	0.29

We claim:

1. A peptide compound of the formula (I) [SEQ. ID. NO. 4]:

1 5 10
 5 Xaa₁ Xaa₂ Xaa₃ Gly Thr Xaa₄ Xaa₅ Xaa₆ Xaa₇ Xaa₈
 15 20
 Ser Lys Gln Xaa₉ Glu Glu Glu Ala Val Arg Leu
 25 30
 10 Xaa₁₀ Xaa₁₁ Xaa₁₂ Xaa₁₃ Leu Lys Asn Gly Gly Xaa₁₄
 35
 Ser Ser Gly Ala Xaa₁₅ Xaa₁₆ Xaa₁₇ Xaa₁₈-Z

wherein Xaa, is His, Arg or Tyr;

Xaa, is Ser, Gly, Ala or Thr;

Xaa, is Asp or Glu;

15 Xaa₄ is Phe, Tyr or naphthylalanine;

Xaa₅ is Thr or Ser;

Xaa₆ is Ser or Thr;

Xaa, is Asp or Glu;

Xaa₈ is Leu, Ile, Val, pentylglycine

Xaa, is Leu, Ile, p

Xaa₁₀ is Phe, Tyr or

Xaa, is Ile, Val, Leu, pentylglycine,

tert-butylglycine or Met;

Xaa_{1,2} is Glu or Asp;

Xaa, is Trp, Phe, Tyr, or naphthylala

Xaa₁₅, Xaa₁₆ and Xaa₁₇ are

Pro, homoproline, 3Hyp, 4

alkylglycine, N-alkylpentylglycine or N-

alkylalanine;

15 DEC, 1941

Z IS -OH OR -NH₂,

with the proviso that the compound does not have the formula of either SEQ. ID. NOS. 1 or 2; and pharmaceutically acceptable salts thereof.

5 2. A compound according to claim 1 wherein Xaa₁ is His or Tyr.

3. A compound according to claim 2 wherein Xaa₁ is His.

4. A compound according to claim 2 wherein Xaa₂ is Gly.

10 5. A compound according to claim 4 wherein Xaa₉ is Leu, pentylglycine or Met.

6. A compound according to claim 5 wherein Xaa₁₃ is Trp or Phe.

15 7. A compound according to claim 6 wherein Xaa₄ is Phe or naphthylalanine; Xaa₁₀ is Phe or naphthylalanine; Xaa₁₁ is Ile or Val and Xaa₁₄, Xaa₁₅, Xaa₁₆ and Xaa₁₇ are independently selected from Pro, homoproline, thioproline or N-alkylalanine.

8. A compound according to claim 7 wherein Xaa₁₈ is Ser or Tyr.

20 9. A compound according to claim 8 wherein Xaa₁₈ is Ser.

10. A compound according to claim 9 wherein Z is
-NH₂.

11. A compound according to claim 1 wherein Xaa₂ is Gly.

12. A compound according to claim 1 wherein Xaa₉ is Leu,
5 pentylglycine or Met.

13. A compound according to claim 1 wherein Xaa₁₃ is Trp
or Phe.

14. A compound according to claim 1 wherein Xaa₄ is Phe
or naphthylalanine; Xaa₁₀ is Phe or naphthylalanine; Xaa₁₁ is
10 Ile or Val and Xaa₁₄, Xaa₁₅, Xaa₁₆ and Xaa₁₇ are independently
selected from Pro, homoproline, thioproline or N-
alkylalanine.

15. A compound according to claim 1 wherein Xaa₁₈ is Ser
or Tyr.

16. A compound according to claim 1 wherein Z is
-NH₂.

17. A compound according to claim 1 which has an amino
acid sequence selected from SEQ. ID. NOS. 5 to 35.

18. A peptide compound of the formula (I) [SEQ. ID. NO. 4] :

1	5	10
5	15	20
5	25	30
10	35	
	Ser Ser Gly Ala Xaa ₁₅ Xaa ₁₆ Xaa ₁₇ Xaa ₁₈ -Z	

Xaa₁ Xaa₂ Xaa₃ Gly Thr Xaa₄ Xaa₅ Xaa₆ Xaa₇ Xaa₈
 Ser Lys Gln Xaa₉ Glu Glu Glu Ala Val Arg Leu
 Xaa₁₀ Xaa₁₁ Xaa₁₂ Xaa₁₃ Leu Lys Asn Gly Gly Xaa₁₄

wherein Xaa₁ is His or Arg;
Xaa₂ is Gly or Ala;
Xaa₃ is Asp or Glu;
Xaa₄ is Phe or naphthylalanine;
Xaa₅ is Thr or Ser;
Xaa₆ is Ser or Thr;
Xaa₇ is Asp or Glu;
Xaa₈ is Leu or pentylglycine;
Xaa₉ is Leu or pentylglycine;
Xaa₁₀ is Phe or naphthylalanine;
Xaa₁₁ is Ile, Val or tert-butylglycine;
Xaa₁₂ is Glu or Asp;
Xaa₁₃ is Trp or Phe;
Xaa₁₄, Xaa₁₅, Xaa₁₆ and Xaa₁₇ are independently
Pro, homoproline, thioproline or
N-methylalanine;
Xaa₁₈ is Ser or Tyr; and
Z is -OH or -NH₂;
with the proviso that the compound does not
have the formula of either SEQ. ID. NOS. 1

or 2;

and pharmaceutically acceptable salts thereof.

19. A compound according to claim 18 which has an amino
5 acid sequence selected from SEQ. ID. NOS. 5, 6, 17, 18, 19,
22, 24, 31, 32 and 35.

20. A compound according to claim 18 which is exendin-3
acid.

10 21. A compound according to claim 18 which is exendin-4
acid.

22. A composition comprising a compound of any of
claims 1-18, 20 or 21 in a pharmaceutically acceptable
carrier.

15 23. A composition comprising a compound of claim 19 in
a pharmaceutically acceptable carrier.

24. A peptide compound of the formula (II) [SEQ. ID.
NO. 40] :

5 10
20 Xaa₁ Xaa₂ Xaa₃ Gly Thr Xaa₄ Xaa₅ Xaa₆ Xaa₇ Xaa₈
15 20
Ser Lys Gln Xaa₉ Glu Glu Glu Ala Val Arg Leu
25 30
Xaa₁₀ Xaa₁₁ Xaa₁₂ Xaa₁₃ Leu X₁ Gly Gly Xaa₁₄
25 35
Ser Ser Gly Ala Xaa₁₅ Xaa₁₆ Xaa₁₇ Xaa₁₈-Z

wherein Xaa_1 is His, Arg, Tyr or 4-imidazopropionyl;
 Xaa_2 is Ser, Gly, Ala or Thr;
 Xaa_3 is Asp or Glu;
 Xaa_4 is Phe, Tyr or naphthylalanine;
5 Xaa_5 is Thr or Ser;
 Xaa_6 is Ser or Thr;
 Xaa_7 is Asp or Glu;
 Xaa_8 is Leu, Ile, Val, pentylglycine or Met;
 Xaa_9 is Leu, Ile, pentylglycine, Val or Met;
10 Xaa_{10} is Phe, Tyr or naphthylalanine;
 Xaa_{11} is Ile, Val, Leu, pentylglycine,
tert-butylglycine or Met;
 Xaa_{12} is Glu or Asp;
 Xaa_{13} is Trp, Phe, Tyr, or naphthylalanine;
15 X_1 is Lys Asn, Asn Lys, Lys-NH^e-R Asn, Asn Lys-NH^e-R
where R is Lys, Arg, C₁-C₁₀ straight chain or
branched alkanoyl or cycloalkylalkanoyl
 Xaa_{14} , Xaa_{15} , Xaa_{16} and Xaa_{17} are independently
Pro, homoproline, 3Hyp, 4Hyp,
20 thioproline, N-alkylglycine,
N-alkylpentylglycine or N-alkylalanine;
 Xaa_{18} is Ser, Thr or Tyr; and
Z is -OH or -NH₂;
with the proviso that the compound does not
25 have the formula of either SEQ. ID. NOS. 1 or 2;
and pharmaceutically acceptable salts thereof.

25. A compound according to claim 24 wherein Xaa_1 is
His, Tyr or 4-imidazopropionyl.

26. A compound according to claim 25 wherein Xaa₁ is His or 4-imidazopropionyl.

27. A compound according to claim 24 wherein Xaa₂ is Gly.

5 28. A compound according to claim 24 wherein Xaa₉ is Leu, pentylglycine or Met.

29. A compound according to claim 24 wherein Xaa₁₃ is Trp or Phe.

10 30. A compound according to claim 24 wherein X₁ is Lys Asn, or Lys-NH^c-R Asn, where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl.

15 31. A compound according to claim 24 wherein Xaa₄ is Phe or naphthylalanine; Xaa₁₀ is Phe or naphthylalanine; Xaa₁₁ is Ile or Val and Xaa₁₄, Xaa₁₅, Xaa₁₆ and Xaa₁₇, are independently selected from Pro, homoproline, thioproline or N-alkylalanine.

32. A compound according to claim 24 wherein Xaa₁₈ is Ser or Tyr.

20 33. A compound according to claim 32 wherein Xaa₁₈ is Ser.

34. A compound according to claim 24 wherein Z is -NH₂.

35. A compound according to claim 24 wherein Xaa₄ is Phe or naphthylalanine; Xaa₁₀ is Phe or naphthylalanine; Xaa₁₁ is Ile or Val, X₁ is Lys Asn, or Lys-NH^e-R Asn, where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl and Xaa₁₄,
5 Xaa₁₅, Xaa₁₆ and Xaa₁₇, are independently selected from Pro, homoproline, thioproline or N-alkylalanine.

36. A compound according to claim 35 wherein Xaa₁₈ is Ser or Tyr.

37. A compound according to claim 35 wherein Z is -NH₂.

10 38. A compound according to claim 22 which has an amino acid sequence selected from SEQ. ID. NOS. 36-39.

39. A composition comprising a compound of any of claims 24-37 in a pharmaceutically acceptable carrier.

15 40. A composition comprising a compound of claim 38 in a pharmaceutically acceptable carrier.

Compound [SEQ. ID. NO.]	Xaa ₁	Xaa ₂	Xaa ₃	Xaa ₄	Xaa ₅	Xaa ₆	Xaa ₇	Xaa ₈	Xaa ₉	Xaa ₁₀
1 (3129) [5]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe
2 (3174) [6]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe
3 (3175) [7]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe
4 (3110) [8]	Tyr	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe
5 (3000) [9]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe
6 [10]	His	Gly	Asp	Phe	Thr	Ser	Asp	Leu	Met	Phe
7 [11]	His	Gly	Glu	naph	Thr	Ser	Asp	Leu	Met	Phe
8 [12]	His	Gly	Glu	Phe	Ser	Ser	Asp	Leu	Met	Phe
9 [13]	His	Gly	Glu	Phe	Ser	Thr	Asp	Leu	Met	Phe
10 [14]	His	Gly	Glu	Phe	Thr	Thr	Asp	Leu	Met	Phe
11 [15]	His	Gly	Glu	Phe	Thr	Ser	Glu	Leu	Met	Phe
12 [16]	His	Gly	Glu	Phe	Thr	Ser	Asp	pGly	Met	Phe
13 [17]	His	Gly	Glu	Phe	Thr	Ser	Asp	pGly	Leu	Phe
14 [18]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	pGly	Phe

Fig. 1

Fig. 1A	Fig. 1B
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Fig. 1A

Fig. 1B

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Compound [SEQ. ID. NO.]	Xaa ₁	Xaa ₂	Xaa ₃	Xaa ₄	Xaa ₅	Xaa ₆	Xaa ₇	Xaa ₈	Xaa ₉	Xaa ₁₀
15 [19]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	pGly	Phe
16 [20]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	naph
17 [21]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe
18 [22]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe
19 [23]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe
20 [24]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe
21 [25]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe
22 [26]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe
23 [27]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe
24 [28]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe
25 [29]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe
26 [30]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe
27 [31]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe
28 [32]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe
29 [33]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe
30 [34]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe
31 [35]	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe

SUBSTITUTE SHEET (RULE 26)

Fig. 1D**Fig. 1C****Fig. 1D** **Fig. 1E**

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Xaa ₁₁	Xaa ₁₂	Xaa ₁₃	Xaa ₁₄	Xaa ₁₅	Xaa ₁₆	Xaa ₁₇	Xaa ₁₈	Z
Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH ₂
Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH ₂
Val	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH ₂
Val	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH ₂
tBuG	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH ₂
tBuG	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH ₂
Ile	Asp	Trp	Pro	Pro	Pro	Pro	Ser	NH ₂
Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH ₂
Ile	Glu	Trp	tPro	tPro	tPro	tPro	Ser	NH ₂
Ile	Glu	Trp	Pro	tPro	tPro	tPro	Ser	NH ₂
Ile	Glu	Trp	hPro	hPro	hPro	hPro	Ser	NH ₂
Ile	Glu	Trp	Pro	hPro	hPro	hPro	Ser	NH ₂
Ile	Glu	Phe	tPro	tPro	tPro	tPro	Ser	NH ₂
Ile	Glu	Phe	hPro	hPro	hPro	hPro	Ser	NH ₂
Ile	Glu	Trp	hPro	hPro	hPro	hPro	Ser	NH ₂
Ile	Glu	Trp	MeAla	MeAla	MeAla	MeAla	Ser	NH ₂
Ile	Glu	Trp	Pro	MeAla	MeAla	MeAla	Ser	NH ₂
Ile	Glu	Phe	MeAla	MeAla	MeAla	MeAla	Ser	NH ₂

Fig. 1E

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His Ser Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser-NH₂
35

Fig. 2

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
5 10 15
Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30
Ser Gly Ala Pro Pro Pro Ser-NH₂
35

Fig. 3

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg-NH₂
20 25 30

Fig 4

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DOSE RESPONSE OF THE GLUCOSE LOWERING EFFECT OF COMPOUND 1
[SEQ. ID. NO. 5] VS. EXENDIN-4 IN db/db MICE

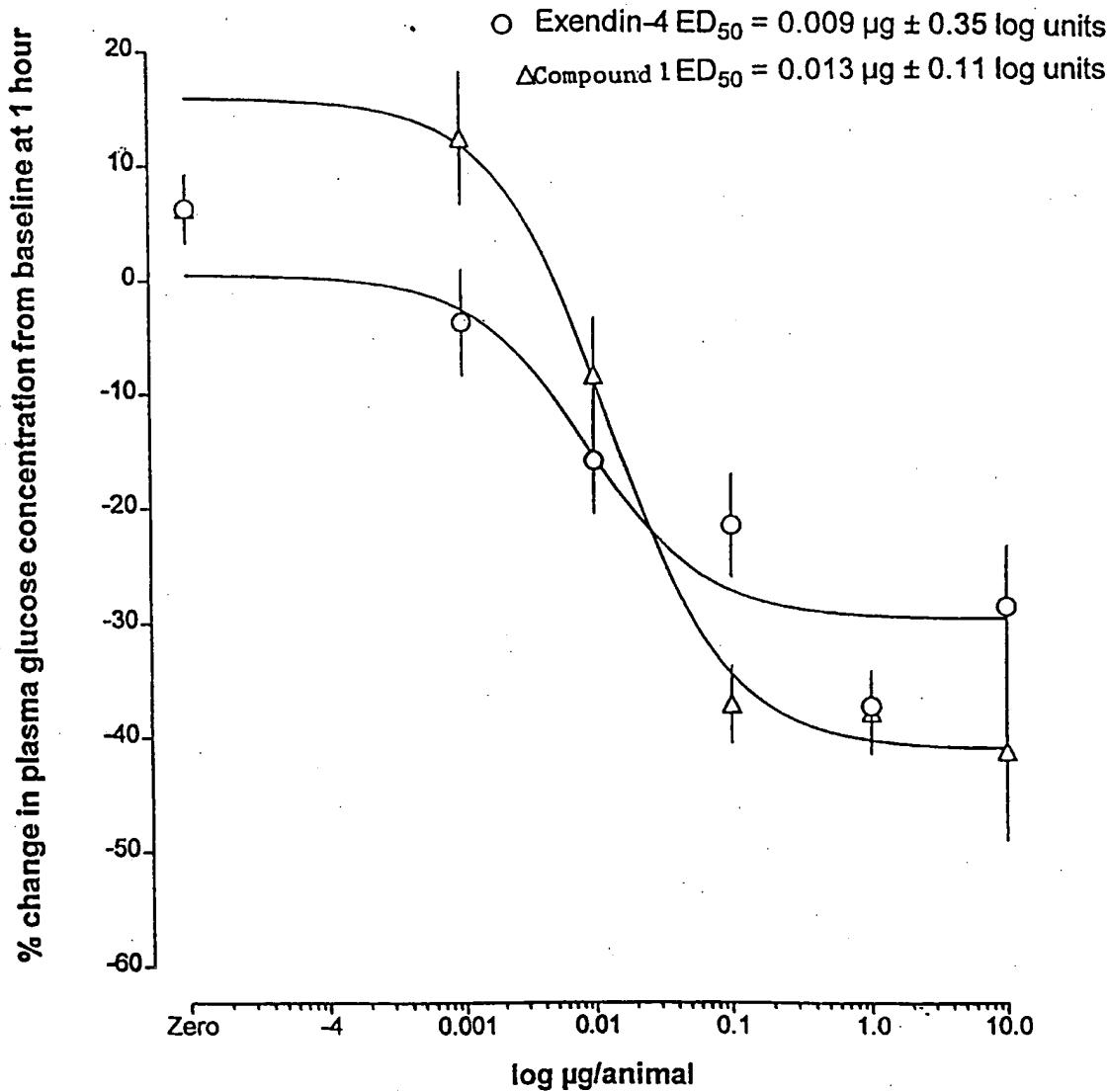


Fig. 5

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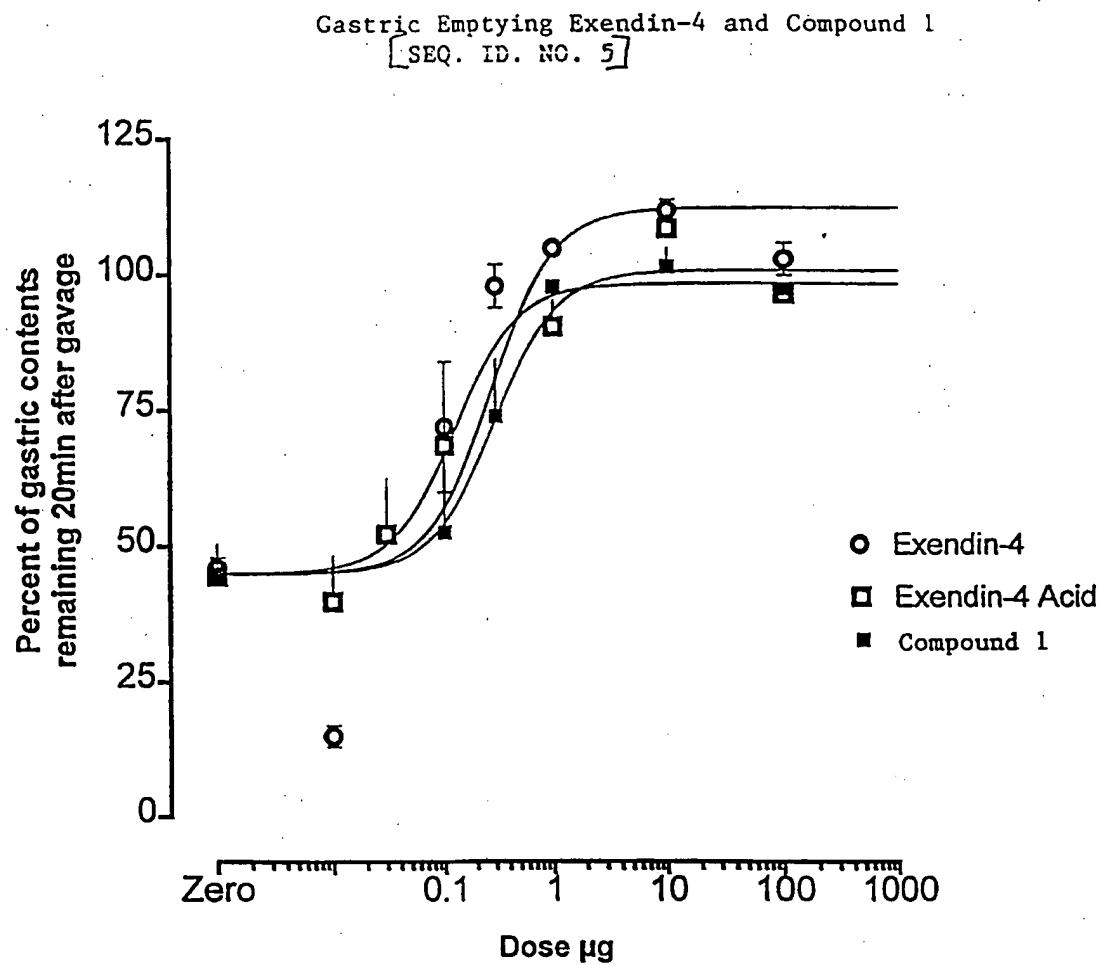


Fig. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/16387

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) A61K 38/16; C07K 14/46
US CL : 514/02, 866; 435/69.1; 530/324

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/02, 866; 435/69.1; 530/324

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN ON LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,424,286 A (ENG) 13 June 1995, co. 5, Table 1.	1-17

Further documents are listed in the continuation of Box C. See patent family annex.

• Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance		
B earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
O document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 29 OCTOBER 1998	Date of mailing of the international search report 14 DEC 1998
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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MICHAEL BORN Telephone No. (703) 308-0956
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/16387

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: 1-17 in part because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The claims cannot be searched in full, because no computer-readable Sequence Listing Form was submitted. In addition, claims 2-16 fail to clearly and concisely define species of peptides. The claims are searched within the scope of the elected species, the peptide of SEQ ID 5.
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-17, SEQ ID No:5

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/16387

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-17 drawn to peptides as defined by the broad claim 1.

Group II, claims 18-23, 38, 40, drawn to peptides as defined by the broad claim 18.

Group III, claim 24-37, 39 drawn to peptides as defined by the broad claim 24.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features because there is no structurally distinctive portion of the structure which is shared by all of the alternative peptide structures.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

The species are as follows: species 1-31 are as specified in the table of Figure 1-1; species 32+ are not specified species resulting from further permutations of residues Xaa1, Xaa2, Xaa4, Xaa7-Xaa18, which comprised of groups of amino acid residues being not obvious substitutions. Claims 1, 18, 24 are generic. Under PCT Rule 13.2, the species lack the same or corresponding special technical features because they do not share any common structure, i.e., there is no structurally distinctive portion of the structure which is shared by all of the alternatives.

Claims 2-16 do not clearly and concisely recite species of the genus of claim 1. Thus, the first named species of the genus appears to be that of SEQ ID No:5.